REMARKS

Status of the Claims

Claims 1-3, 6-12, 18-25, 28, 37 and 38 are currently pending in this application. Claims 1-3, 6-12, 18-25, 28, 37 and 38 are rejected in the Office Action mailed on October 29, 2010. In this amendment, claim 1 is amended to clarify the invention. Support for the amendment is found in the specification and in original claim 1. Thus, no new matter has been added. Upon entry of the amendment, claims 1-3, 6-12, 18-25, 28, 37 and 38 will be pending and subject to further examination. Entry of the amendment and reconsideration on the merits in view of the following comments is respectfully requested.

Claim Rejections - 35 USC § 112

Claim 1 is rejected under 35 U.S.C. § 112, second paragraph, as allegedly being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. Claim 1 has been amended to remove the "or virus" language and therefore, this rejection should properly be withdrawn.

Claim Rejections - 35 USC § 103

Dauer in View of Iinuma or O'Neill, Grevelding and Wong

Claims 1-3, 6-9, 12, 18, 20-25, 28 and 37 are rejected under 35 U.S.C. § 103(a) as allegedly being obvious over Dauer et al. (*Biotechnol. Bioeng.*, 37:1021-1028 (1991), hereinafter "Dauer") in view of Iinuma et al. (*Int. J. Cancer* 2000, 89:337-344, hereinafter "Iinuma"), Grevelding et al. (*Nucleic Acids Res.*, 24(20):4100-4101 (1996), hereinafter "Grevelding") and Wong et al. (U.S. Patent No. 5,734,020, hereinafter "Wong").

Claims 1-3, 6-9, 12, 18, 20-25, 28 and 38 are rejected under 35 U.S.C. § 103(a) as allegedly being obvious over Dauer in view of O'Neill et al. (U.S. Patent 6,187,546, hereinafter "O'Neill"), Grevelding and Wong.

Dauer allegedly teaches a method of isolating cells using magnetic particles. With regard to claim 1, Dauer allegedly teaches a process for amplifying a nucleic acid of a target cell or virus, which process comprises: a) contacting a sample containing or suspected of containing a target cell or virus with a magnetic microbead not comprising a biomolecule that binds to said target cell or virus with high specificity (p. 1024, col. 2, where baker's yeast were the target cells and where the magnetic microbead comprises a magnetic "seed" comprising ferromagnetic gamma-iron oxide or maghemite (Fe_2O_3); see Table 1); b) allowing said target cell or virus, if present in said sample, to bind to said magnetic microbead to form a conjugate between said target cell or virus and said magnetic microbead (Figure 6, where the process of mixing, binding and separation are depicted; p. 1025. col. 2, and where the pH is used to control binding to the particles and then release of the particles); c) separating said conjugate from other undesirable constituents via a magnetic force to isolate said target cell or virus from said sample (Figure 6E, where the conjugate between the magnetic particle and the cells are separated from the sample), wherein said biomolecule is selected from the group consisting of an antibody, an amino acid, a peptide, a protein, a nucleoside, a nucleotide, an oligonucleotide, a nucleic acid, a vitamin, a monosaccharide, an oligosaccharide, a carbohydrate, a lipid and a complex thereof (Table 1, p. 1024, col. 2, where the magnetic particle is not coated with a biomolecule or other affinity group).

The Office acknowledges that Dauer does not teach that the magnetic microbeads is modified to comprise a hydroxyl, arboxyl or an epoxyl group, as required by claims 1-3, 6-9, 12, 18, 24-25, 28, 37 and 38. To cure this deficiency of Dauer, the Office cites Wong, which allegedly teaches that the magnetic microbeads is modified to comprise a hydroxyl, arboxyl or an epoxyl group (col. 2, lines 11-24).

The Office acknowledges that Dauer does not teach that the target cells can comprise leukocytes, as required by claims 1-3, 6-9, 12, 18, 24-25, 28 and 37. To cure this deficiency of Dauer, the Office cites Iinuma, which allegedly teaches that leukocytes can be specifically targeted by magnetic beads comprising anti-CD45 monoclonal antibodies (p. 337, col. 2).

Similarly, the Office acknowledges that Dauer does not teach that the target cells can comprise epithelial cells, as required by claims 1-3, 6-9, 12-13, 18, 24-25, 28 and 38. To cure this deficiency of Dauer, the Office cites O'Neill, which allegedly teaches a saliva sample containing or suspected of containing an epithelial cell (col. 20, where epithelial cells are exfoliated into saliva or sputum), wherein the epithelial cell is enriched and isolated by binding to a magnetic particle (col. 20, lines 32-35, where epithelial cells are enriched using magnetic particle sorting).

The Office further acknowledges that Dauer does not explicitly teach that the cells can be applied to an amplification system. To cure this deficiency of Dauer, the Office cites Grevelding, which allegedly teaches a method comprising d) applying said separated conjugate to a nucleic acid amplification system to amplify a nucleic acid from said target cell or virus, wherein said process does not comprise a step of lysing said target cell or virus to release said nucleic acid prior to applying said separated conjugate to said nucleic acid amplification system (Abstract, p. 4100, col. 1, where the technique of PCR is applied to whole organisms and has been applied to yeast and bacteria).

The Office argues that it would have been *prima facie* obvious to one of ordinary skill in the art at the time the invention was made to have analyzed the target cells of Iinuma using the method of separation taught by Dauer to arrive at the claimed invention with a reasonable expectation for success. Iinuma allegedly teaches that "prepared cells were resuspended in 80 pl of BSA-PBS mixed with 20 pi of CD45 microbeads for 15 min at 4°C and passed down the MACS column" (p. 338, col. 1). Therefore, the Office argues that one of ordinary skill in the art at the time the invention was made would have been motivated to have analyzed the target cells of Iinuma using the method of separation taught by Dauer to arrive at the claimed invention with a reasonable expectation for success.

The Office argues that it also would have been *prima facie* obvious to one of ordinary skill in the art at the time the invention was made to have extended the teachings of Dauer and Inuma to include the additional functional groups of Wong to arrive at the claimed invention with a reasonable expectation for success. Wong allegedly teaches "porous inorganic magnetic materials,

preferably siliceous materials, surface modified to provide functional groups such as amino, hydroxyl, carboxyl, epoxy, aldehyde, sulfhydryl, phenyl or long chain alkyl groups to facilitate the chemical and/or physical attachment of biological molecules and other moieties, e.g., enzymes, antibodies, oligopeptides, oligonucleotides, oligosaccharides or cells. Surface modification to create such functionality may be accomplished by coating with organic silanes. Alternate methods for providing derivatized or functional group containing surfaces on the magnetic products of this invention include U.S. Pat. Nos. 3,983,299 and 4,554,088" (col. 2, lines 11-24). Therefore, the Office argues that one of ordinary skill in the art at the time the invention was made would have been motivated to have extended the teachings of Dauer and Inuma to include the additional functional groups of Wong to arrive at the claimed invention with a reasonable expectation for success.

Furthermore, the Office argues that it would have been *prima facie* obvious to one of ordinary skill in the art at the time the invention was made to have adjusted the method of Dauer to include further analysis of the captured and released cells using PCR amplification as taught by Grevelding to arrive at the claimed invention with a reasonable expectation for success. Grevelding allegedly teaches that "recently protocols were introduced that allow PCR amplification without DNA extraction" and that "PCR amplification is possible from whole, undissected larvae and adults of the fruitfly *Drosophila melanogaster* and the blood fluke, *Schistosoma mansoni* without preceding DNA isolation." Regarding the applicability of the method to other types of cells, Grevelding allegedly teaches that "[s]ince it worked both with an organism covered by a tegument as well as one surrounded by a chitineous cuticle, it is expected that it should also be applicable for a variety of other eukaryotic organisms" (p. 4101, col. 1). The Office takes the position that while Grevelding teaches isolation from whole organisms, the technique of amplification directly from cells without prior DNA extraction is clearly supported by the teachings of Grevelding. Therefore, the Office argues that one of ordinary skill in the art would have been motivated to have adjusted the method of Dauer to include further analysis of the captured and released cells using PCR amplification as taught by Grevelding to arrive at the claimed invention with a reasonable expectation for success.

Applicants respectfully traverse these rejections for the reasons set forth below.

The obviousness analysis under 35 U.S.C. § 103(a) requires the consideration of the scope and content of the prior art, the level of skill in the relevant art, and the differences between the prior art and the claimed subject matter must be considered. *KSR Int'l Co. v. Teleflex Inc.*, 127 S.Ct. 1727 (2007) (*citing Graham v. John Deere Co.*, 383 U.S. 1, 17 (1966)). Rejections on obviousness grounds cannot be sustained by mere conclusory statements. *In re Kahn*, 441 F.3d 977, 987-88 (Fed. Cir. 2007) (citations omitted). Critical elements of the invention as a whole which clearly distinguish the entire invention from the prior art references cannot be ignored. *Panduit Corp. v. Dennison Manufacturing Co.*, 1 U.S.P.Q.2d 1593, 1597 (Fed. Cir.), *cert. denied*, 481 U.S. 1052 (1987).

As presented in the previous Response, the Office fails to provide a reason to combine Dauer, which teaches non-specific separation of yeast cells, with Iinuma or O'Neill, both of which teach highly specific immunomagnetic separation of mammalian cells. *See KSR*, 550 U.S. at 420. In response, the Office asserts that the features upon which Applicants rely (i.e., mammalian cells) are not recited in the rejected claims. Applicants respectfully disagree. Although the previous arguments presented by Applicants are directed at the differences between yeast and mammalian cells, the same arguments can be made at the differences between yeast and leukocytes or epithelial cells, which are recited in the presently claimed invention. Similar to mammalian cells, the leukocyte or epithelial cell membrane is composed primarily of lipids, such as phospholipids, glycolipids and cholesterol, and the content of polysaccharides in a leukocyte or epithelial cell outer membrane layer is significantly lower than in the yeast cell wall. Accordingly, based on the disclosure of Dauer that non-specific magnetic separation was effective for large-scale yeast separation, a person skilled in the art at the time of the invention could not have reasonably expected that the same technique would have been successful in leukocytes or epithelial cells.

The Office further states that Applicants were arguing inoperability of the combination of references and points out: "while the differences between yeast and epithelial cells may be significant, Applicant successfully uses magnetic microparticle beads in separation of these cells

that are structurally indistinguishable from the magnetic seed particles taught by Dauer." Applicants respectfully disagree. Applicants did not argue that combining the use of high gradient magnetic separation (HGMS) to separate nonmagnetic microorganisms such as the baker's yeast taught by Dauer with leukocytes or epithelial cells is inoperable. Rather, Applicants were arguing that given the significant differences between yeast and leukocytes or epithelial cells, a person of ordinary skill in the art would not have a reasonable expectation of success to modify the method of Dauer to arrive at the presently claimed invention. Therefore, the Office fails to identify the reason why a person of ordinary skill in the art would have combined the prior art elements in the manner claimed.

Further, Applicants respectfully submit that combining Dauer with Iinuma or O'Neill would change the principle of operation of the method by Dauer. *See* MPEP § 2143.01(VI). Dauer teaches the use of HGMS to separate nonmagnetic microorganisms such as the baker's yeast from solution by a technique known as seeding, whereby fine magnetic particles are adhered to the cells' surfaces, making them magnetic and amenable to magnetic separation. (*See* Abstract.) Dauer further teaches that technique may be used to recover microorganisms from dilute process streams and is particularly well suited to the final clean-up and isolation of proprietary or hazardous organisms. (*See* Dauer at page 1027, right col.) Thus, Dauer is primarily concerned with large-scale magnetic separation of microorganisms from solution. Iinuma teaches highly specific separation of $CD45^+$ cells using magnetic microbeads coated with anti-CD45 antibodies (page 338). Similarly, O'Neill teaches highly specific separation of exfoliated cells in sputum or saliva using magnetic beads coated with Ber-EP4 antibody specific for epithelial cells (col. 20, lines 32-35). Neither Iinuma nor O'Neill teaches or even suggests nonspecific or low-specificity magnetic separation of leukocytes or epithelial cells. The suggested combination of Dauer with Iinuma or O'Neill would require a substantial reconstruction and redesign of the elements shown in Dauer as well as a change in the basic principle under which the Dauer method was designed to operate. *See In re Ratti*, 270 F.2d 810, 813 (CCPA 1959) (cited in MPEP § 2143.01(VI)).

Similarly, the Office fails to identify a reason why a person of ordinary skill in the art would have combined Duer and Wong to arrive at the presently claimed invention. Wong teaches a

method for making porous inorganic magnetic materials including any glass, silica gel or alumina, useful, e.g., in the separation of biochemical moieties or biological molecules or fragments thereof from a surrounding medium, in the synthesis of peptides and oligonucleotides, in the purification of mRNA or poly (dA) directly after synthesis and in DNA assay procedures in various immunoassay procedures for enzyme immobilization and in sample preparation (col. 1, lines 57-65). Wong does not teach or even suggest nonspecific or low-specificity magnetic separation of leukocytes or epithelial cells. Therefore, a person of ordinary skill in the art would not be motivated to combine the teachings of Duer, which is directed to the use of HGMS to separate nonmagnetic microorganisms such as the baker's yeast, with those of Wong, which is directed to the use of porous inorganic magnetic materials in the purification of biological molecules.

Also critical to analysis under 35 U.S.C. § 103 is avoidance of impermissible hindsight. Rather the analysis must focus on what the references would suggest to one of ordinary skill in the art at the time the invention was made, who is normally guided by the then-accepted wisdom in the art. *See W.L. Gore & Assoc., Inc. v. Garlock, Inc.*, 721 F.2d 1540 (Fed. Cir. 1983), *cert. denied*, 469 U.S. 851 (1984). Applicants respectfully submit that but for the use of impermissible hindsight, a person of ordinary skill in the art would have no reason to combine the teachings of Dauer, which teaches non-specific separation of yeast cells, with those of Iinuma or O'Neill, both of which teach highly specific immunomagnetic separation of mammalian cells, and those of Wong, which teaches the use of porous inorganic magnetic materials in the purification of biological molecules. Therefore, the only possible explanation for the Examiner's obviousness rejection is the use of impermissible hindsight.

In view of the above, there was no reasonable motivation to combine the teachings of Dauer with those of Iinuma or O'Neill, Grevelding and Wong, but for the use of impermissible hindsight, and combining Dauer with Iinuma or O'Neill would change the principle of operation of the method by Dauer. Therefore, the Office has failed to establish a *prima facie* case of obviousness. Accordingly, it is respectfully submitted that these rejections under 35 U.S.C. § 103(a) may properly be withdrawn.

Dauer in View of Iinuma, Grevelding and Wong, and Further in View of Lopez-Sabater

Claims 5 and 29 are rejected under 35 U.S.C. § 103(a) as allegedly being obvious over Dauer in view of Iinuma, Grevelding and Wong as applied to claims 1-3, 6-9, 12-13, 18, 20-25, 28 and 37 above, and further in view of Lopez-Sabater et al. (*Lett. Appl. Microbiol.*, 24:101-104 (1997)).

As noted in the previous Response, this rejection is moot in view of the earlier cancellations of claims 5 and 29.

Dauer in View of Iinuma, Grevelding and Wong, and Further in View of Ughelstad

Claim 10 is rejected under 35 U.S.C. § 103(a) as allegedly being obvious over Dauer in view of Iinuma, Grevelding and Wong as applied to claims 1-3, 6-9, 12-13, 18, 20-25, 28 and 37 above, and further in view of Ughelstad et al. (WO 83/103920 (1983), hereinafter "Ughelstad").

The Office acknowledges that Dauer does not explicitly teach that the magnetic beads can be made of Fe_3O_4. To cure this deficiency of Dauer, the Office cites Ughelstad, which allegedly teaches magnetic beads for use in separation wherein the metal composition is Fe_3O_4.

The Office argues that it would have been *prima facie* obvious to one of ordinary skill in the art at the time the invention was made to have applied the specific teachings of Ughelstad to the particles of Dauer to arrive at the claimed invention with a reasonable expectation for success. Dauer allegedly states: "The magnetic seed is a ferromagnetic γ-iron oxide (γ-Fe_2O_3) or maghemite" (p. 1024, col. 2). Ughelstad teaches wherein the method composition comprises Fe_3O_4 specifically (see p. 9). Therefore, the Office argues that one of ordinary skill in the art at the time the invention was made would have been motivated to have applied the specific teachings of Ughelstad to the particles of Dauer to arrive at the claimed invention with a reasonable expectation for success.

The teachings of Dauer, Iinuma, Grevelding and Wong have been briefly discussed above. Ughelstad teaches various magnetic polymer particles prepared by treating compact or

porous polymer particles with a solution of iron salts and, optionally, salts of other metals which are capable of forming magnetic ferrites, in which the solution swells or penetrates into the particles.

Ughelstad fails to provide any teachings that would cure the deficiencies of Dauer, Iinuma, Grevelding and Wong as discussed above. Much like Dauer, Iinuma, Wong and Grevelding, Ughelstad does not provide any reasonable expectation of success for direct PCR amplification on mammalian cells, particularly leukocytes or epithelial cells. Therefore, the Office has failed to establish a *prima facie* case of obviousness. Accordingly, it is respectfully submitted that this rejection under 35 U.S.C. § 103(a) may properly be withdrawn.

Dauer in View of O'Neill, Grevelding and Wong, and Further in View of Dzieglewska

Claims 11 and 19 are rejected under 35 U.S.C. 103(a) as allegedly being obvious over Dauer in view of O'Neill, Grevelding and Wong as applied to claims 1-3, 6-9, 12-13, 18, 20-25, 28 and 38, and further in view of Dzieglewska (WO 98/51693 (1998), hereinafter "Dzieglewska").

The Office acknowledges that Dauer does not explicitly teach the additional limitations of claims 11 and 19. To cure these deficiencies of Dauer, the Office cites Dzieglewska, which allegedly teaches magnetic microbead having a diameter ranging from about 5 to about 50,000 manometers (claim 11); an automated method of nucleic acid isolation (claim 19); and a target cell comprising a bacteria or eukaryotic cell and can be obtained from a urine sample).

The Office argues that it would have been *prima facie* obvious to one of ordinary skill in the art at the time the invention was made to have adjusted the teachings of Dauer to the include elements of Dzieglewska to arrive at the claimed invention with a reasonable expectation for success. Although the Office acknowledges that Dzieglewska teaches a method comprising lysis of cells prior to amplification, the Office argues that the elements of the claims represented by Dzieglewska are obvious in combination with the teaching of Dauer, O'Neill, Grevelding and Wong. Accordingly, the Office concludes that one of ordinary skill in the art at the time the invention was made would have been motivated to have adjusted the teachings of Dauer, O'Neill,

Grevelding and Wong to include elements of Dzieglewska to arrive at the claimed invention with a reasonable expectation for success.

The teachings of Dauer, O'Neill, Grevelding and Wong have been briefly discussed above. A careful review of Dzieglewska reveals that it fails to provide any teachings that would cure the deficiencies of Dauer, O'Neill, Grevelding and Wong as discussed above. For example, much like Dauer, O'Neill, Grevelding and Wong, Dzieglewska does not provide any reasonable expectation of success for direct PCR amplification on mammalian cells, particularly leukocytes or epithelial cells. Therefore, the Office has failed to establish a *prima facie* case of obviousness. Accordingly, it is respectfully submitted that this rejection under 35 U.S.C. § 103(a) may properly be withdrawn.

In view of the above, each of the presently pending claims in this application is believed to be in immediate condition for allowance. Accordingly, the Examiner is respectfully requested to withdraw the outstanding rejection of the claims and to pass this application to issue. If it is determined that a telephone conference would expedite the prosecution of this application, the Examiner is invited to telephone the undersigned at the number given below.

In the event the U.S. Patent and Trademark office determines that an extension and/or other relief is required, applicant petitions for any required relief including extensions of time and authorizes the Commissioner to charge the cost of such petitions and/or other fees due in connection with the filing of this document to **Deposit Account No. 03-1952** referencing docket No. 514572000700. However, the Commissioner is not authorized to charge the cost of the issue fee to the Deposit Account.

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